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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/315,292

05/20/1999

CLARENCE FRANK BENNETT

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KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER

BOWMAN, AMY HUDSON

ART UNIT

PAPER NUMBER

1635

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/315,292	BENNETT ET AL.	
	Examiner	Art Unit	
	AMY BOWMAN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 August 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 99-121 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 99-121 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 20 May 1999 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's response filed 8/1/08 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 5/1/08 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action

Applicant has added claims 120 and 121. Therefore, claims 99-121 are pending in the instant application.

Applicant's arguments and/or amendments filed on 8/1/08, with respect to the rejections under 35 U.S.C. 112, 2nd paragraph and 35 U.S.C. 112, 1st paragraph (in-part) have been fully considered and are persuasive. Therefore, these rejections have been withdrawn. However, the rejection under 35 U.S.C. 103(a) is pending as explained below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 99-119 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

Art Unit: 1635

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **THIS IS A NEW MATTER REJECTION.**

Applicant's arguments regarding support for the phrases "about 1 to about 5 microns" and "about 15 to about 25 nucleotides in length" are convincing.

Applicant asserts that the specification supports a "plurality" of 2'-O-methoxyethyl nucleosides, as recited in instant claim 99; and "at least about half" 2'-O-methoxyethyl nucleosides as recited in instant claims 108 and 118. Applicant argues that a "plurality" refers to more than one, which applicants have disclosed in the specification as filed. However, applicant does not point to such support in the specification as filed to define "plurality" or to even utilize the term "plurality" in any manner. The specific examples of oligonucleotides comprising more than one 2'-O-methoxyethyl modification on page 34 are certainly not representative of any plurality, are not supportive of more than one, and are not supportive of at least about half. The specific examples that fall within the instant ranges represent species of a much broader genus that is being instantly claimed. One of skill would not be able to recognize that applicant was in possession of the instant ranges based upon the examples pointed to by applicant because the instant claims are much broader than what is disclosed.

There is no support for these claim limitations in the claimed priority documents. Therefore, the effective filing date of claims 99-119 is considered, for purposes of prior art, to be 5/20/99, which is the filing date of the instant application.

Art Unit: 1635

A review of the specification, and particularly the pages pointed to by applicant, does not reveal support for where the various claim amendments are found. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim limitation added in the amended claims filed on 2/15/08.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

Art Unit: 1635

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 99-121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyce et al. (WO 96/40266) (cited and of record on PTO-892 mailed on 5/10/06), in view of Nicklin et al. (WO 98/09633) (cited and of record on PTO-892 mailed on 5/10/06) and Levesque et al. (Molecular Pharmacology, 51, 1997, pages 209-216) (cited and of record on the PTO-892 mailed on 5/1/08). Newly added claims 120 and 121 are included herein as they recite modifications that were previously included in the rejection.

Nyce et al. teach that antisense oligonucleotides may be administered to the lungs of a patient by any suitable means, but preferably administered by generating an aerosol comprised of respirable particles, the respirable particles comprised of the antisense compound, which particles the subject inhales (see page 10).

Nyce et al. teach that respirable antisense oligonucleotides can be formulated to be liquid or solid (see page 10). Liquid compositions comprise the antisense compound and sterile, pyrogen free water or saline solution (see page 9, for example). Nyce et al. teach that suitable formulations for delivery include powders (see page 12). Nyce et al. teach that respirable antisense oligonucleotides can be formulated into powders and effectively delivered with a metered dose inhaler. Nyce et al. teach methylphosphonate and phosphorothioate linkages to render respirable antisense oligonucleotides more stable *in vivo* (see page 7).

Nyce et al. teach that particles comprised of antisense compound should be of respirable size that is particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. Nyce et al. teach that in general, particles ranging from about .5 to 10 microns in size are respirable (see page 10). Therefore, Nyce et al. teach respirable particles “about 1 to about 5 microns”, as instantly recited. Nyce et al. teach that the antisense oligonucleotides may be of any suitable length, e.g. from about 10 to 60 nucleotides in length (see page 8) and specifically exemplify an 18-mer and a 21-mer (see pages 14 and 15) that is phosphorothioated.

Nyce et al. teach a method of administering the aerosolized antisense oligonucleotides to animals *in vivo* (see page 16, for example) and teach uptake of the oligonucleotide in the lungs. Nyce et al. teach methods of treating asthma via administering an antisense oligonucleotide to the lung of a subject (see page 3).

Nyce et al. do not teach 2'-O-methoxyethyl or 5-methylcytosine modifications.

Nicklin et al. teach antisense oligonucleotides and teach that modification of antisense oligonucleotides confers increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target (see page 2). Nicklin et al. teach 2' modifications including 2'-alkoxyalkoxy, 2'-O-methoxyethyl, and 2'-O-dialkylaminoalkoxy modifications (see pages 2-4). Nicklin et al. teach phosphorothioate, methylphosphonate, and non-phosphorous containing linkage modifications (see pages 4 and 5). Nicklin et al. teach that in certain especially preferred embodiments, all backbone linkages are phosphorothioate linkages. Nicklin

Art Unit: 1635

et al. teach that preferred bases include at least one 5-methylcytosine. Nicklin et al. teach chimeric configurations having one or more regions of 2'-modified nucleotides, particularly 2'-methoxyethoxy nucleotides (see page 4). Nicklin et al. teach antisense oligonucleotides that are 20 nucleotides in length (see pages 5-10, for example).

Levesque et al. teach that a 20-mer phosphorothioate antisense oligonucleotide which contains 2'-methoxyethyl modifications reduced target mRNA expression, wherein the mismatched control had no effect (see summary, page 209).

It would have been obvious to incorporate 2'-O-methoxyethyl modifications, as taught by Nicklin et al. and Levesque et al. and/or 5-methylcytosine modifications, as taught by Nicklin et al. into the antisense oligonucleotides taught by Nyce et al.

One would have been motivated to incorporate 2'-O-methoxyethyl or 5-methylcytosine modifications into the oligonucleotides of the method of Nyce et al. because Nicklin et al. teach that such modifications confer increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target. Furthermore, Levesque et al. teach that a 20-mer phosphorothioate antisense oligonucleotide which contains 2'-methoxyethyl modifications reduced target mRNA expression, wherein the mismatched control had no effect. Since Nyce et al. teach other modifications, such as incorporation of phosphorothioates, in order to render the respirable antisense oligonucleotides more stable *in vivo*, one would have been motivated to incorporate other modifications as well that were also known in the art to enhance oligonucleotide activity, as evidenced by Nicklin et al. and Levesque et al.

With regards to the level/degree of modification, it would have been prima facie obvious to perform routine optimization to determine the optimal level of modification, as noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the particular range used was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

The instant claims require various broad quantities of each type of modification. It was known in the art at the time the invention was made to deliver oligonucleotides to the lung of mammals via introducing aerosolized oligonucleotides of the instantly recited size range and particle size range that are modified, as taught by Nyce et al. The only difference between the instantly recited method and the method of Nyce et al. is the specific types of chemical modifications, wherein each of the instantly recited chemical modifications were known in the art to benefit the stability of antisense oligonucleotides, as evidenced by Nyce et al., Levesque et al., and Nicklin et al. It is within the realm of routine optimization to incorporate various quantities of the known chemical modifications, as it was known in the art to incorporate the chemical modifications into chimeric configurations, as evidenced by Nicklin et al. Additionally, Levesque et al. specifically teaches successful target inhibition when utilizing a 20-mer antisense oligonucleotide with phosphorothioates and 2'-methoxyethyls. Therefore, it would have

Art Unit: 1635

been obvious to try to the instantly recited combination of modifications at different levels/quantities in view of the teachings of Nicklin et al., Levesque et al. and Nyce et al.

Finally, one would have a reasonable expectation of success that the chemical modifications taught by Nicklin et al. and Levesque et al. would benefit the antisense oligonucleotides of Nyce et al. because each of the instantly recited modifications were known in the art at the time the invention was made to enhance the activity of antisense oligonucleotides, as evidenced by Nicklin et al., Levesque et al. and Nyce et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicant asserts that the examiner must articulate a reason why one of skill in the art would modify the oligonucleotide of Nyce to arrive at the claimed invention. Although the examiner clearly set forth that one would have been motivated to incorporate 2'-O-methoxyethyl and 5-methylcytosine modifications into the oligonucleotides of the method of Nyce because Nicklin teaches that such modifications confer increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target; applicant asserts that Nicklin is not limited strictly to these two types of modifications. Nicklin et al. is evidence that each of the instantly recited modifications were known in the art to be modifications that are incorporated into oligonucleotides to enhance the stability therein. Since Nyce teaches modifying the

Art Unit: 1635

oligonucleotides of the method of Nyce, one would have certainly been motivated to utilize routine optimization to incorporate other modifications that were known to benefit oligonucleotides as well. Nicklin does not need to specifically point strictly to these two types of modifications to render the instant modifications obvious.

Nicklin et al. specifically teaches an “especially preferred embodiment” wherein the oligonucleotide is a chimeric oligonucleotide having one or more regions with 2'-deoxynucleotides and one or more regions with 2'-modified nucleotides, preferably 2'-alkoxynucleotides, wherein the one or more deoxynucleotide regions preferably have phosphorothioate backbone linkages. Nicklin teaches that these chimeric oligonucleotides preferably comprise a region of 2'-deoxynucleotides flanked by two regions of 2'-modified nucleotides (see pages 4 and 5).

Applicant argues that the previously cited Yu et al. reference which was relied upon for teaching gapmer configurations which are no longer being claimed teaches away from the instant invention because Yu et al. tested the anti-HIV activity of 8 different 25 base oligonucleotides and reported that the oligonucleotides with the longer central deoxy gap were better than those with the shorter gap or that did not have a central gap. Applicant's interpretation of the teachings of Yu et al. are considered erroneous because the comparison being made by Yu et al. is not a straight comparison of gap size, but is rather a comparison of the activity of gapmers with deoxyribonucleoside phosphorothioates flanked by stretches of 2'-O-methyl ribonucleoside phosphoric diester linkages (oligos 2-4) to hybrid oligonucleotides with deoxyribonucleoside phosphorothioates flanked by segments of contiguous 2'-O-methyl

Art Unit: 1635

ribonucleoside phosphorothioate linkages (oligo 6). Furthermore, Yu et al. teaches that different configurations have shown preferential results, included inverted hybrids and conclude that the studies demonstrate that it is possible to perform therapeutic optimizations of the antisense oligonucleotides by subtle structural changes in the nucleoside sugar residue and internucleotidic phosphate linkages of the active molecule. Yu et al. further concludes that knowledge gained from these studies should help guide the development of future generation of antisense oligonucleotides as therapeutic agents (see page 1691, column 1). Therefore, the teachings of Yu et al. support that the number of nucleotides of the wings and gaps, as well as configurations of known modifications in general, are considered to be routine optimizations.

It is noted that applicant has previously argued that the modifications of Yu et al. are not 2'-O-methoxyethyl modifications, but are rather 2'-O-methyl modifications, but applicant is now claiming that Yu et al. teaches away from the instant invention, which are conflicting arguments. Furthermore, Yu et al. certainly does not teach away from incorporating any plurality of 2'-O-methoxyethyl modifications, embracing even the incorporation of two and does not teach away from the instant modifications that are not directed to different configurations of gapmers as taught by Yu et al. Applicant is making an erroneous conclusion that Yu et al. teaches away from 2'-O-modifications, which is simply not the case. The teachings of Yu et al. are specific to optimizing the activity of gapmer oligonucleotides, which are not commensurate in scope with the instant claims that do not require such a configuration.

Levesque et al. teach that a 20-mer phosphorothioate antisense oligonucleotide which contains 2'-methoxyethyl modifications reduced target mRNA expression, wherein the mismatched control had no effect (see summary, page 209). Although applicant asserts that Levesque does not contain a direct comparison between modified and unmodified oligos, this is not necessary because the modifications were known to enhance the stability of oligonucleotides, as evidenced by the instant references.

Applicant notes that the examiner did not address the teachings of Yu et al. in the last office action, but rather stated that the rejection was withdrawn because Yu et al. was relied upon for teaching gapmers which is no longer an element of the instant claims. Applicant amended the claims thereby resulting in a different rejection, as the claims no longer recited the element that Yu was relied upon for. Applicant's specific arguments are addressed herein even though this article is not relied upon in the rejection.

Applicant argues unexpected results although the results are not unexpected when compared to the state of the art. Applicant relies upon an erroneous conclusion that Yu et al. teaches away from 2'-modifications to conclude that incorporation of a plurality of 2'-O-methoxyethyl modifications yielding active molecules is an unexpected result. The teachings of Yu et al. are addressed above. Incorporation of a plurality of 2'-O-methoxyethyl modifications as well as each of the other structural elements of the instant claims in any configuration within the oligonucleotide is considered within the realm of routine optimization of the oligonucleotides of Nyce and is certainly not an unexpected result in view of the scope of the instant claims.

Art Unit: 1635

In conclusion, Nyce teaches the instant method with modified oligonucleotides, wherein 2'-O-methoxyethyl and 5-methylcytosine modifications were known in the art to benefit antisense oligonucleotides. Within the breadth of the instant claims, it would have been obvious to routinely optimize the oligonucleotides of the method of Nyce via incorporating the modifications that were known to benefit antisense with the expectation of successful molecules.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

Art Unit: 1635

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AMY BOWMAN
Examiner
Art Unit 1635

/AMY BOWMAN/
Examiner, Art Unit 1635